



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
-----------------	-------------	----------------------	---------------------

09/034,286 03/04/98 FALB

D 7853-114

HM12/0624

EXAMINER

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036

NGUYEN, D

ART UNIT	PAPER NUMBER
----------	--------------

1633

TD

DATE MAILED:

06/24/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/034,286	Applicant(s) Falb
	Examiner Dave Nguyen	Group Art Unit 1633

Responsive to communication(s) filed on August 6, 1998, and June 7, 1999

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 53-83 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 53-83 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 9

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948 *substituted* PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The specification has been amended by the preliminary amendment dated August 6, 1998.

Claims 1-52 have been canceled, and claims 53-83 have been added by the preliminary amendment dated June 7, 1999.

Claims 53-83 are pending to which the following grounds of rejection are applicable.

Objection to the Specification

The specification is objected to under 37CFR 1.52(b), which requires that the pages of the specification be numbered starting with "1". Pages i-iv of the specification do not conform with the arrangement of the specification according to MPEP 608.01(a), particularly since the item (b) "Cross Reference to Related Applications" does not appear on the first paragraph of the specification, and since the title headings appear both at page i and page 1 of the specification. It is suggested that pages i-iv should be deleted or removed from the specification.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to a "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) Title of the Invention.
- (b) Cross - Reference to Related Applications.
- (c) Statement Regarding Federally Sponsored Research or Development.
- (d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
- (e) Background of the Invention.
 - 1. Field of the Invention.
 - 2. Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (f) Brief Summary of the Invention.
- (g) Brief Description of the Several Views of the Drawing(s).
- (h) Detailed Description of the Invention.
- (i) Claim or Claims (commencing on a separate sheet).
- (j) Abstract of the Disclosure (commencing on a separate sheet).
- (k) Drawings.
- (l) Sequence Listing (see 37 CFR 1.821 - 1.825).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 64, 66, 67, 76, and 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp. 32639-32645 (also available at www.uspto.gov).

Claims 62, 64, and 66 recite that the polynucleotide sequences claimed in claims 61, 63, and 65 are down-regulated in endothelial cells under shear stress and encode any protein which inhibits TFG- β signaling. Claim 67 claims all unspecified human polynucleotide sequences that encode the proteins recited in claims 62, 64, and 66. Claims 62, 64, 66, 76, and 77 require that the polynucleotide sequences encode any polynucleotide down-regulated in endothelial cells under shear stress, and encode any protein that inhibits a TGF- β signaling. However, the specification only discloses a human rchd534-long gene (cDNA and/or mRNA sequences) which is down-regulated in endothelial cells under shear stress (SEQ ID NO: 64 or SEQ ID NO: 65 which is encoded by SEQ ID NO: 64). In analyzing whether the written description requirement is met for genus claim, it is first determined whether a representative number of species have been described by their complete structure. In this case, SEQ ID NO. 64 is the only species whose complete structure and function is disclosed. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence). In this case, the only identifying characteristics are the "down-regulated" of the rchd534-long gene in endothelial cells under shear

stress and its involvement in a TGF- β signaling pathway. While the application and the claims recite the "hybridization" characteristics of all of the mammalian genes other than the rchd534-long gene and fragments thereof, it is not apparent how one skilled in the art determines what are exactly the sequence structures of all claimed DNA sequences encoding functionally active polypeptides other than the rchd534-long gene, particularly since the problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence of the rchd534-long gene (SEQ ID No: 64) and in turn utilizing the sequence structures to ascertain the sequence structures of all other mammalian genes that have the same functions as the rchd534-long gene is complex and unpredictable (Ngo *et al.*, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.*, (ed.), Birkhauser, Boston, MA, pp. 492-495). This limited information is not sufficient to reasonably convey to one skilled in the art that Applicant was in possession of functionally active genes other than the rchd534-long gene (SEQ ID NO: 64) and its functional fragments thereof (the N-domain of SEQ ID NO: 65, for example).

Claims 62, 64, 66, 67, 76, and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to DNA sequences encoding SEQ ID NO: 65 which includes SEQ ID NO: 64. The specification does not reasonably provide enablement for claims directed to other polynucleotide sequences as recited in the claims. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims encompass non-disclosed DNA sequences that hybridize to DNA sequences contained in SEQ ID NO: 64 or DNA sequences encoding SEQ ID NO: 65 (claims 61, 63, and 65), wherein the DNA sequences are down-regulated in endothelial cells under shear stress and encode unspecified proteins that inhibit TGF- β signaling. When given their broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including unspecified genes encoding for an unspecified protein involving in a TGF- β signaling pathway. However, the specification fails to provide an enabling disclosure for what such polynucleotides would comprise and how one skilled in the art determines which of the unspecified polynucleotide sequences as claimed encodes a protein(s) involving in a TGF- β signaling pathway, without

undue experimentation, particularly on the basis of applicant's disclosure. While the application contemplates that all of the claimed polynucleotide sequences have a biological function or activity, e.g., proteins involving in a TGF- β signaling pathway, the application does not provide sufficient guidance and/or evidence for one skilled in the art to determine which of the claimed polynucleotide sequences exhibits a biological function disclosed in the application. More specifically as to claimed DNA sequences other than DNA sequences encoding SEQ ID NO: 65, the specification only provides guidance for the use of the elected polynucleotides for further experimentation in the elaboration of potential proteins that might be encoded by the claimed polynucleotides. The first use represents an invitation to experiment wherein the skilled artisan is invited to elaborate a functional use for DNA sequence that hybridize to the rchd534-long gene. In addition, the invention as defined by the claims is drawn to undisclosed nucleic acids that are not required to have any particular degree of sequence identity and may not necessarily encode any putative proteins that the nucleic acids encompassed by the claimed invention might encode. Thus, given the lack of guidance and direction in regard to what the polynucleotides defined by the claims would comprise and how one would use such, the artisan would be required to exercise undue experimentation in practice of the invention. Note that the Court of Appeals for the Federal Circuit has ruled that claims that embrace a large number of species of polynucleotide sequences without proper guidance in the application as to how to make and use such polynucleotides do not meet the requirements of 35 U.S.C. § 112, first paragraph, *Amgen v Chugai* (18 USPQ2d 1016 (Fed. Cir. 1991)).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54, 57, 61, 62, and 67-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54, 57 and claims dependent therefrom are indefinite in the recitation of "the amino acid unique to the rchd534-long protein" because it is not apparent as to what are the

metes and bounds of the "unique". Note that "the amino acid unique" also lacks an antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54, 57, 61-66, 68-73, 75, and 77-83 are rejected under 35 U.S.C. 102(a) as being anticipated by *Imamura et al.* (Nature 389, pp. 622-626, 1997).

The claims are directed to any polynucleotide sequence that hybridizes under unspecified stringent conditions to the rchd534-long gene (SEQ ID NO: 64), vectors, cDNA sequences, and host cells containing the polynucleotide sequences. A method of producing a gene product encoded by the polynucleotide sequence is also claimed in claim 77. Claims 54 and 57 also recite DNA sequence comprising a polypeptide coding region unique to the coding region of SEQ ID NO: 64. *Imamura et al.* disclose a cultured mammalian cell containing a cDNA clone having an expression vector which comprises a polynucleotide sequence (isolated from a heart cDNA library) which has 93% match to the rchd534-long gene.

Absent evidence to the contrary, the polynucleotide sequences, host cells, and vectors of *Imamura et al.* has all of the properties cited in the claims, e.g., hybridizes under the recited stringent condition, and comprise sequences being unique to the coding region of SEQ ID NO: 64.

Claims 63, 64, and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by *Riggins et al.* (Gene Bank Database, AN: U59914, published November 1, 1996).

The claims are directed to any polynucleotide sequence that hybridizes under the

Serial Number: 09/034,268
Art Unit: 1633

recited highly stringent conditions to any polynucleotide sequence that encodes the amino acid sequence set forth in SEQ ID NO: 65.

Riggins *et al.* teach a polynucleotide sequence that encodes a Mad homolog smad6

mRNA, wherein the polynucleotide sequence (isolated and sequenced from a human chromosome) has 99.3% identity to nucleotides 972-1812 of SEQ ID NO: 64 of the application (SEQ ID NO: 64 encodes the rchd534-long protein).

Absent evidence to the contrary, the polynucleotide sequence of Riggins *et al.* hybridizes to SEQ ID NO: 64, and has all of the properties cited in the claims.

Claims 54, 57, 61-73, 75, and 77-83 are rejected under 35 U.S.C. 102(a) as being anticipated by Hata *et al.* (Genes & Development 12, pp. 186-197, published January 15, 1998).

The claims are directed to any polynucleotide sequence that hybridizes under the recited stringent conditions. The claims are also directed to vectors, eukaryotic host cells containing the polynucleotide sequence. Claims 54 and 57 also recite DNA sequence comprising any polypeptide coding region unique to the coding region of SEQ ID NO: 64.

Hata *et al.* teach a method using vectors and eukaryotic host cells for generating a cDNA sequence (the Smad6 gene) that encodes a polypeptide sequence which is 99.9% identical to SEQ ID NO: 65 (which is also encoded by the cDNA sequence contained in the plasmid clone pHL6T11A, pages 195 and 196) also see the search Result attached to the PTO-892 form).

Methods for making recombinant proteins encoded by the Smad6 gene is also disclosed in Hata *et al.* Figure 7 at page 194 of Hata *et al.* provides evidence demonstrating that the Smad6 gene product inhibits a TGF- β signaling.

Absent evidence to the contrary, the DNA sequence, vectors, host cells, methods for producing the Smad6 gene product of Hata *et al.* have all of the properties cited in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 53-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hata *et al.* (Genes & Development 12, pp. 186-197, published January 15, 1998) in view of Moren (Gene Bank Database, AN: AF043640, published February 4, 1998), and Blakely *et al.* (US Pat No. 5,418,162).

The claims are directed to any polynucleotide sequence that encodes the polypeptide sequence set forth in SEQ ID NO: 65. The claims are also directed to vectors, prokaryotic and eukaryotic host cells containing any polynucleotide sequence that encodes the polypeptide sequence set forth in SEQ ID NO: 65.

Hata *et al.* teach a method using vectors and eukaryotic host cells for generating a cDNA sequence (the Smad6 gene) that encodes a polypeptide sequence which is 99.9% identical to SEQ ID NO: 65 (which is also encoded by the cDNA sequence contained in the plasmid clone pH6T11A, pages 195 and 196) also see the search Result attached to the PTO-892 form). The Smad6 gene has one nucleotide mismatch, e.g., Asn → Asp, at base 997 as compared to SEQ ID NO: 64 of this application. Methods for making recombinant proteins encoded by the Smad6 gene is also disclosed in Hata *et al.* Figure 7 at page 194 of Hata *et al.* provides evidence demonstrating that the Smad6 gene product inhibits a TGF- β signaling. Hata *et al.* do not teach the exact sequences as set forth in SEQ ID Nos 64 and 65, nor do Hata *et al.* teach prokaryotic host cells containing the Smad6 gene.

However, at the time the invention was made, Moren teaches a complete mRNA sequence encoding the human Smad6 gene (obtained from chromosome 15) which has 100% match to the cDNA coding sequence set forth in SEQ ID NO: 64 or the rchd534-long gene.

In addition, Blakely *et al.* disclose that it is routine to employ prokaryotic host cells to produce recombinant proteins from a known gene (column 5, lines 35-45)

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the difference by one conservative substitution in the Smad6 gene of Hata *et al.* as

compared to SEQ ID NO: 64 of this application would either be the result of sequencing artifact or allelic variation, and thus, the difference is *de minimis*, particularly since the encoded polypeptide sequence of Hata *et al.* is 99.9% identical to the encoded polypeptide sequence of the rchd534-long gene (see the sequence comparison disclosed in the search results).

It would also have been obvious for one of ordinary skill in the art to have employed the Smad6 gene disclosed in Moren in the method of Hata *et al.* to produce recombinant Smad6 gene products, as taught by Hata *et al.*, with a reasonable expectation of success, particularly since both coding sequences disclosed in Moren *et al.* and Hata *et al.* encode a Smad6 gene product.

It would also have been obvious for one of ordinary skill in the art to have employed prokaryotic cells to produce Smad6 gene products in the method of Hata *et al.*, with a reasonable expectation of success, particularly since it is known in the art that prokaryotic cells and eukaryotic cells are routinely employed in the art to produce recombinant proteins.

Thus, the claimed invention as a whole was *prima facie* obvious.

Double patenting rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 63 and 67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,834,248. Although

Serial Number: 09/034,280
Art Unit: 1633

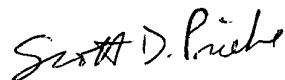
the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-7 of the '248 patent recite human DNA sequences encoding SEQ ID NO: 37 (SEQ ID NO: 36, for example) that is identical to residues 972 to 1752 of SEQ ID NO: 34 of this instant application.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is (703) 305-2024.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Brian Stanton* may be reached at (703) 308-2801.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.



Scott D. Priebe, Ph.D
Patent Examiner